-- 53. A recombinant immunotoxin polypeptide or a pharmaceutically acceptable salt thereof according to claim 52, wherein the CD3-binding fragment comprises a single-chain Fv of UCHT-1. --

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-- 54. A recombinant immunotoxin polypeptide selected from polypeptides having residues 1-601, 2-601 or 3-601 of SEQ. ID. NO:1 or a pharmaceutically acceptable salt thereof. --

REMARKS

Claims 1-7, 9-16 and 29-34 have been cancelled and new claims 35-54 have been added to substitute therefor.

The first line of the specification has been updated.

New corrected formal drawings are submitted herewith.

Included herewith on a separate page is a new Abstract wherein the word "said" has been replaced with the word "the".

Claims 31-33 (corresponding to new claims 50 and 51) stand rejected under 35 U.S.C. §112, first paragraph, for insufficient written description.

Applicants' arguments in response to the rejection, filed January 16, 2002, were considered but not found persuasive.

It is stated in the Office Action that:

> No "unambiguous sequence information" is provided regarding the antibodies with variable regions at least 90% identical to the variable region of UCHT-1 or antibodies about 90% as effective as UCHT-1 for binding human CD3, and no single specific method for determining sequence identity is disclosed, indeed, the specification indicates that *any* method is sufficient. Further, while stringent hybridization conditions have been disclosed, no "tangible structural features" defining the claimed polypeptides have been recited in the claims, thus, the claims encompass polypeptides as short as a few amino acids; it is the Examiner's position then that said polypeptides have not been sufficiently described in the specification.

It is respectfully pointed out that Applicants' specification does provide unambiguous sequence information regarding the variable region of UCHT-1. The last paragraph on page 20 of application specifies the variable region in great detail. Specifically, the variable region of UCHT-1

is taught as comprising "residue 3 to 112 (light chain) and 128 to 249 (heavy chain) of SEQ. ID. NO:1 herein." This is unambiguous sequence information.

Regarding the "identity" requirement of claim 51, contrary to what is stated in the Office Action, Applicant's specification does teach a specific method for determining sequence identity. The last paragraph of page 22 of the specification states:

> As a practical matter, whether any particular polypeptide sequence is at least 80%, 90%, or at least 95%, "identical to" another polypeptide can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, Wis. 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% or the total number of amino acid residues in the reference sequence are allowed.

Applicant's claim 51 now specifically recites that the percent identity is determined by use of the Bestfit program.

Regarding the determination of antibodies that are about 90% as effective as UCHT-1 for binding human CD3, Applicant's specification on page 21 states:

> These antibodies include a monoclonal antibody competing with, e.g., UCHT-1, for binding to human CD3 antigen at least about 80%, and more preferably at least about 90%, as effectively on a molar basis as UCHT-1, and having at least one sequence segment of at least five amino acids of human origin. By "specific binding affinity" is meant binding affinity determined by noncovalent interactions such as hydrophobic bonds, salt linkages, and hydrogen bonds on the surface of binding molecules.

Moreover, determining the binding affinity of a given antibody for CD3 relative to UCHT-1 is well within the skill in the art, see, for example, the competitive FACS assay for binding in the article by J.M. Hexham et al., Molecular Immunology, 38, 397-408, 2001, included herewith. From the information available in the art and the teachings in the specification, it is submitted that one skilled in the art would have no problem determining those monoclonal antibodies that are about 90% as effective as UCHT-1 for binding human CD3.

Although it is acknowledged in the Office Action that "stringent conditions" is adequately defined in Applicant's specification, it is stated that no "tangible structural features" are recited in the

claim. It is respectfully pointed out that claims 49 and 50 recite SEQ. ID. NO:2 and that claim 51 recites the variable region of UCHT-1 (which, as pointed out earlier, has a specific sequence as disclosed in Applicant's specification). Again, the specific disclosed sequences constitute tangible structural features.

It is further stated in the Office Action that, the claims encompass polypeptides as short as a few amino acids. Applicants respectfully submit that this is not the case. Claim 50 now requires a polypeptide encoded by the complement of a nucleotide sequence having at least 300 bases. Support for this amendment is on page 38 of the specification, third paragraph. Thus, a polypeptide encoded by such a nucleotide sequence must necessarily have substantially more than a few amino acids. Similarly, claim 51 requires an antibody having a variable region at least 90% identical to the variable region of UCHT-1, such an antibody must necessarily have more than a few amino acids. Furthermore, Applicant's claims 50 and 51 are directed to an immunotoxin. Polypeptides, with only a few amino acids, would not be immunotoxins.

Claims 31-33 (now 50 and 51) stand rejected under 35 U.S.C. §112, first paragraph, for a lack of enablement.

Applicants traverse this rejection.

It is stated in the Office Action that:

> . . . the specification, while being enabling for, a recombinant immunotoxin polypeptide consisting of the polypeptide encoded by the nucleotide sequence of SEQ. ID. NO:2, does not reasonably provide enablement for:
>
> A) a recombinant immunotoxin polypeptide comprising the polypeptide encoded by a nucleotide sequence which hybridizes with the nucleotide sequence of SEQ. ID. NO:2 under stringent hybridization conditions, or
>
> B) a recombinant immunotoxin polypeptide comprising the polypeptide encoded by any nucleotide sequence which hybridizes to the nucleotide sequence of Claim 31 under stringent hybridization conditions, or
>
> C) a recombinant immunotoxin polypeptide comprising an antibody having a variable region which is at least about 90% identical to the variable region of UCHT-1 and is at least about 90% as effective as UCHT-1 for binding human CD3.

It is further stated:

> Regarding A) and B), a sequence which hybridizes to SEQ. ID. NO:2 would be its complementary DNA sequence. A polypeptide encoded by

said complementary DNA sequence would not encode the recombinant immunotoxin of the instant claims, but rather a random collection of amino acids. Said random collection of amino acids would be unlikely to function as an immunotoxin and would thus be considered highly unpredictable. Said unpredictability would necessitate undue experimentation as there would be no particular expectation of success.

Regarding Parts A) and B) of the rejection, it is respectfully pointed out that Applicants are no longer claiming a polypeptide encoded by a sequence which hybridizes to SEQ ID. NO:2 (claim 32). Applicant's claim 51 is similar to old claim 33 in that it claims a polypeptide encoded by the complement of a sequence which hybridizes to SEQ. ID. NO:2. Therefore, such a polypeptide would not be a random collection of amino acids. It is further pointed out that if the polypeptide of claim 51 does not function as an immunotoxin, it is not within the scope of claim 51.

Regarding Part C) of the rejection, the Office Action cites the unpredictable nature of substituted antibodies. While Applicants agree that small changes in an antibody sequence can have a dramatic effect on activity, Applicants have provided sufficient information in order for one to practice the invention as claimed.

It is submitted that the scope and detail of Applicants' disclosure do fairly provide suitable procedures for obtaining the immunotoxins of the invention. It is respectfully submitted that Applicants' disclosure is in compliance with the enablement requirement of 35 U.S.C. §112. That the work described in the specification may be labor-intensive and time-consuming does not negative Applicants' compliance with the enablement requirement (see, Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) and *In re* Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)).

Similarly, while possibly labor-intensive or time-consuming, it would be well within the range of normal experimentation by a worker of ordinary skill in the art, using the procedures disclosed by Applicants, to prepare immunotoxins not exemplified in the specification. The skill in the art at the time of filing the application was very high. One skilled in the art could easily determine whether or not a particular polypeptide has 90% identity to UCHT-1, whether such a polypeptide is at least about 90% as effective as UCHT-1 for binding UCHT-1, and whether such a polypeptide functions as an immunotoxin.

Claims 1-7, 9-16 and 30-34 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Applicants have amended their claims to use the "pharmaceutically acceptable salt thereof" language, as suggested by the Examiner, and have corrected claim dependency. Therefore, this rejection is now believed to be moot.

Claims 1-7, 9-16, 29-30 and 33-34 (now claims 35-49 and 51-54) stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,103,235 in view of Kreitman et al., Cancer Biology, Vol. 6, pp. 297-306 (1995) and Krectmis et al., Leukemia of Lymphoma, Vol. 13, pp. 1-10 (1994).

Applicants traverse this rejection.

As stated in Applicants previous response, the bits and pieces of Applicants' claimed immunotoxin may be present in the prior art, but the requisite incentive or motivation to combine these bits and pieces is lacking.

It is stated in the Office Action that Kreitman et al., (1994) teaches that immunotoxic antibody-PE40 fusion proteins and immunotoxic antibody-DT fusion proteins are functionally interchangable. It is respectfully pointed out that this reference does not teach such interchangability.

The Kreitman et al. paper compares the activities of several immunotoxins directed against Tac (not CD3 as presently claimed). The data in Table 34 of the reference show the ability of different patients blood cells to be killed by the different immunotoxins. There is no predictability or pattern to the results. That is, *a priori*, one could not predict the effectiveness of a given PE-Tac immunotoxin on a given cell population by knowing the activity of a given DT-Tac immunotoxin on that cell population.

Moreover, the Examiner's attention is directed to the reference by Batra et al., Mol. Cell. Biol., Vol. 11, No. 4, pp. 2200-2205 (1991). This reference compares two single-chain anti-human transferrin receptor immunotoxins, one with DT (designated DT388-anti-TFR (Fv)) and one with PE (designated TFR (Fv) - PE40). In the Discussion section, it is concluded that:

> "Unexpectedly, large differences in the activities of the two single-chain immunotoxins were observed. On some cell lines (A431, KB and MCF7) anti-TFR (Fv) - PE40 was at least 100-fold more active than DT-388-anti-TFR (Fv). On two cell lines (HUT102 and HT29), DT388-anti-TFR (Fv), was about three-fold more active."

Thus, one skilled in the art having the prior art before him could not *a priori* reasonably predict the effectiveness for a particular use of an anti-CD3-PE based immunotoxin with the knowledge that an anti-CD3-DT based immunotoxin is effective for that use.

It is submitted that Applicants specification and claims are in proper form. Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, first and second paragraphs, and under 35 U.S.C. §103(a), and that pending claims 35-54 be passed to allowance.

Respectfully submitted,

Novartis Pharmaceuticals Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6765

Thomas R. Savitsky
Attorney for Applicants
Reg. No. 31,661

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ABSTRACT

Recombinant immunotoxin polypeptides are described comprising a CD3-binding domain and a Pseudomonas exotoxin mutant, and in particular, comprising a single chain (sc) Fv as the CD3-binding moiety. A preferred species of the invention comprises scFv(UCHT-1)-PE38. Also disclosed are methods for the preparation of the immunotoxins; functionally equivalent immunotoxins which are intermediates in the preparation of the immunotoxins of the invention, as well as polynucleotide and oligonucleotide intermediates; methods for the prevention and/or treatment of transplant rejection and induction of tolerance, as well as treatment of autoimmune and other immune disorders, using the immunotoxins or pharmaceutically acceptable salts thereof; and pharmaceutical compositions comprising the immunotoxins or pharmaceutically acceptable salts thereof.

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

--This application claims the benefit of provisional application No. 60/183,056 filed October 7, 1999; provisional application No. ~~60/~~60/266,285 filed January 25, 1999 ~~(converted from Application No. 09/236,968)~~; and provisional application No. 60/183,059 filed January 15, 1999.--

ABSTRACT

Recombinant immunotoxin polypeptides are described comprising a CD3-binding domain and a Pseudomonas exotoxin mutant, and in particular, comprising a single chain (sc) Fv as the CD3-binding moiety. A preferred species of the invention comprises scFv(UCHT-1)-PE38. Also disclosed are methods for the preparation of ~~said~~ the immunotoxins; functionally equivalent immunotoxins which are intermediates in the preparation of the immunotoxins of the invention, as well as polynucleotide and oligonucleotide intermediates; methods for the prevention and/or treatment of transplant rejection and induction of tolerance, as well as treatment of autoimmune and other immune disorders, using the immunotoxins or pharmaceutically acceptable salts thereof; and pharmaceutical compositions comprising the immunotoxins or pharmaceutically acceptable salts thereof.